REMARKS

Applicant has amended the title of the present application to read "Immunogenic Polypeptides for Inducing Anti-self IgE Responses." The title as amended more fully describes the presently claimed invention, and is consistent with the title of the patent application from which it claims priority. No new matter has been added.

Claim 25-28 are pending and were rejected. In light of the following remarks, Applicant respectfully requests reconsideration and allowance of claims 25-28.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 25-28 under 35 U.S.C. § 112, first paragraph as not being enabled. The Examiner stated that while the specification is enabling for polypeptides consisting of amino acid sequences such as those shown in Figures 2A and 2B, the specification does not reasonably provide enablement for any polypeptide "comprising" at least any two CH3 IgE domains and any CH4 IgE domain that is heterologous to at least one of the CH3 IgE domains. The Examiner further stated that the specification does not reasonably provide enablement for any polypeptide "comprising" at least two rat CH3 IgE domains or at least two human CH3 IgE domains and any CH4 IgE domain, or any polypeptide "comprising" at least any two CH3 IgE domains and an opossum CH4 IgE domain. Citing the scope of the claims, the amount of guidance provided, the lack of sufficient working examples, the unpredictability in the art, and the amount of experimentation required, the Examiner concluded that the specification disclosure is insufficient to enable a person of skill in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Applicant respectfully disagrees. The test for enablement is whether one skilled in the art at the time Applicant filed the present application would have been able to make and use the claimed invention based on the disclosures in the specification coupled with the information known in the art without "undue" experimentation. *See, e.g.*, MPEP § 2164.01. Many factual considerations must be weighed when determining whether "undue" experimentation would be required, including: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of

the art, (6) the amount of direction or guidance provided, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. *See, In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All the evidence related to each of these factors must be considered, and any conclusion of nonenablement must be based on the evidence as a whole. MPEP § 2164.01(a).

Analysis of all the related evidence clearly reveals that Applicant's specification as filed is such that one skilled in the art would have been able to make and use the claimed invention without "undue" experimentation. First, the presently claimed invention recites a polypeptide comprising at least two CH3 IgE domains and a CH4 IgE domain that is heterologous to at least one of the CH3 IgE domains, and the following analysis must be with respect to such a claim breadth. Second, the nature of the claimed invention is a polypeptide that can be used to generate an anti-self IgE response in a mammal. Given the nature of the invention, the state of the prior art and the relative skill of those in the art must be determined with respect to chimeric polypeptide technology and the use of chimeric IgE polypeptides to elicit mammalian anti-self IgE responses. *See, e.g.*, MPEP § 2164.05(a).

Third, the state of the prior art can be characterized as follows. The present application is a continuation of application serial no. 09/401,636 (the '636 application). Those skilled in the art at the time the '636 application was filed understood IgE antibodies and their involvement with allergies. Since the early 1980's, IgE antibodies have been cloned from many species. For example, the Aveskogh *et al.* reference (*Eur. J. Immunol.*, 28:2738-2750 (1998)) discloses an alignment of IgE sequences from mouse, rat, sheep, pig, dog, horse, opossum, chimpanzee, orangutan, and human. Applicant notes that the disclosure of the Aveskogh *et al.* reference is incorporated by reference into the disclosure of the present application. *See*, page 22, lines 26-27, and page 7, lines 18-19. Further, the state of the art with respect to chimeric polypeptides at the time Applicant filed was such that polypeptides were routinely engineered to contain whatever domains and sequences (*e.g.*, tag sequences) were desired by a particular researcher or technician. Techniques for cloning homologs of polypeptides such as IgE also were routine, as evidenced by the number of IgE sequences presented in Applicant's specification and in publications such as the Aveskogh *et al.* reference.

Fourth, the relative skill of those in the art at the time the parent application was filed can

be characterized as being quite high. Clearly, those skilled in the art would have been well aware of the types of methods needed to obtain IgE sequences from different species, including non-placental species, and to combine these sequences into chimeric polypeptides. For example, those skilled in the art would have been able to perform well known molecular biology techniques such as library screening, molecular cloning, and PCR cloning to obtain IgE sequences from species beyond those disclosed in Applicant's specification or in the Aveskogh *et al.* reference, for example. In fact, Dr. Lars Hellman stated in a declaration (copy attached) filed in the '636 application that a graduate student and technician in his laboratory were able to use a platypus IgE nucleic acid fragment and standard library screening techniques to obtain an IgE sequence from echidna. Further, those skilled in the art would have been readily able to combine IgE domains from different species into chimeric polypeptides. In fact, the Nissim *et al.* group (*see, e.g., EMBO J.*, 10:101-107 (1991); reference AAAAAAA on the Form 1449 submitted on August 3, 2004) combined IgE domains from mouse and human to make several chimeric IgE polypeptides that were used to evaluate the regions of IgE involved in receptor binding. Thus, those skilled in the art at the time Applicant filed the present application can be considered molecular biologists who understood IgE antibodies and the techniques required for obtaining and combining IgE sequences.

Fifth, the Examiner appears to allege that the art is so unpredictable that those skilled in the art would have expected that all the guidance provided by Applicant's specification applies only to those polypeptides having the sequences shown in Figures 2A and 2B. Applicant respectfully disagrees, and submits that those skilled in the art would have been able to make and use a polypeptide containing at least two IgE CH3 domains and an IgE CH4 domain heterologous to at least one of the CH3 domains without undue experimentation. For example, those skilled in the art would have been able to obtain CH3 and CH4 IgE sequences from any two or more species and would have been able to combine those IgE sequences to form a chimeric polypeptide. This is particularly true given that Applicant's specification discloses IgE sequences from human, rat, pig, dog, opossum, and platypus. In addition, the Aveskogh *et al.* reference, which as explained above is incorporated by reference into the disclosure of the present application, discloses IgE sequences from mouse, rat, sheep, pig, dog, horse, opossum, chimpanzee, orangutan, and human. Clearly, one skilled in the art reading Applicant's

specification would not have concluded that IgE sequences are so unpredictable that "undue" experimentation would be required to find an IgE sequence from a species other than those provided in Applicant's specification. In fact, the information known about IgE antibodies at the time the parent application was filed does not support the Examiner's allegation that obtaining and combining IgE sequences to produce chimeric IgE polypeptides was unpredictable.

Sixth, Applicant's specification provides ample guidance to enable a skilled artisan to make and use the presently claimed polypeptides. For example, Applicant's specification discloses combining two or more CH3 IgE domains with a heterologous CH4 IgE domain to produce a chimeric IgE polypeptide. *See, e.g.*, Example 7 on pages 26-27. Applicant's specification also teaches that a nucleic acid molecule for expressing such a chimeric IgE polypeptide can be produced using common molecular cloning techniques. *See, e.g.*, page 19, lines 19-26. In addition, Applicant's specification discloses methods for administering chimeric IgE polypeptides to a mammal, and demonstrates that such polypeptides can be used to induce anti-self IgE responses. *See, e.g.*, page 21, lines 10-21 and Example 5 on pages 24-25. Given these data alone, one skilled in the art would have appreciated that chimeric IgE polypeptides can induce anti-self IgE responses within mammals having low, medium, or high levels of IgE. Further, one skilled in the art would have appreciated from these data that chimeric IgE polypeptides can be used to induce clearly detectable anti-IgE responses. Thus, Applicant's specification provides those of skill in the art with the ability to use the presently claimed polypeptides to induce an anti-IgE response within a mammal. Taken together, the guidance provided throughout Applicant's specification demonstrates that one skilled in the art could readily envision the structure of a large number of chimeric IgE polypeptides that can be made and used to induce an anti-IgE response within a mammal.

Seventh, Applicant's specification provides working examples that clearly demonstrate enablement of the present claims. For example, Applicant's specification provides working examples that demonstrate the successful construction and use of an ORO immunogenic polypeptide as discussed above. Applicant's specification also discloses making polypeptides designated ORORO and 6his-ORRRORO-6his. *See*, Example 7 on pages 26-27. The straightforward construction and use of the ORO immunogenic polypeptide, together with the successful construction of the ORORO and 6his-ORRRORO-6his polypeptides, demonstrates

that no undue experimentation would have been required for a person of ordinary skill in the art to make and use chimeric IgE polypeptides having various combinations of CH3 and CH4 IgE domains.

Eighth, the quantity of experimentation needed to make and use the presently claimed invention is not unreasonable given the state of the art, the high level of skill within the art, and the guidance provided by Applicant's specification. One skilled in the art easily could have followed the teachings of Applicant's specification to obtain CH3 and CH4 IgE sequences from two or more species and combine those sequences to make a polypeptide. One skilled in the art also could have readily administered the polypeptide to a mammal and evaluated the mammal to determine whether an anti-self IgE response was induced. As indicated above, the ORO polypeptide induced an anti-self IgE response that was easily detected using routine procedures. For example, an ELISA was used to measure anti-IgE titers. Thus, any molecular biologist familiar with immunology and IgE molecules could have performed all of the tasks required to make and use the presently claimed invention without undue experimentation. Applicant notes that enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

In light of the above, it is clear that the presently claimed invention is enabled. The following paragraphs address other comments made by the Examiner in the outstanding Office Action.

On page 3 of the Office Action, the Examiner stated that the "specification does not teach how to make all polypeptides as set forth in claims 25-28 because there is insufficient guidance as to the structure of the polypeptide without the amino acid sequence" (emphasis added). Applicant respectfully notes that the specification is not required to set forth structures for the entire scope of claimed polypeptides. In fact, the legal standard of enablement requires Applicant's specification to enable a person of ordinary skill to make and use the presently claimed polypeptides without undue experimentation. Applicant's specification satisfies the enablement requirement. Again, Applicant's specification provides the primary amino acid structure for IgE domains from human, rat, mouse, pig, dog, opossum, and platypus, which represent a broad spectrum of mammalian diversity. Applicant's specification also discloses

methods for making chimeric polypeptides containing heterologous CH3 and CH4 IgE domains, as well as methods for determining whether a chimeric IgE polypeptide elicits an anti-self IgE response when administered to a mammal. Given Applicant's specification, the state of the art, and the level of skill in the art as discussed above, a skilled artisan would have been able to use routine techniques to obtain CH3 and CH4 IgE sequences from two or more species, to combine them to make a polypeptide as recited in present claim 25, and to determine whether the polypeptides resulted in an anti-self IgE response in a mammal. No undue experimentation would have been required. Thus, the present claims are fully enabled.

The Examiner also stated on page 3 of the Office Action that the term "comprising" expands the claimed polypeptide to include additional amino acids at either or both ends, but that there is insufficient guidance as to which amino acids are to be included. Applicant respectfully submits that the present specification provides multiple examples of amino acid sequences that can be added to the CH3 and CH4 IgE domains of the presently claimed polypeptides. For example, one of skill in the art reading Applicant's specification would have appreciated that an IgE CH2 domain can be included in a chimeric polypeptide as presently claimed. One of skill also would have appreciated that a tag sequence (*e.g.*, a signal sequence and/or a histidine tag) can be included in the claimed polypeptides. *See, e.g.*, Applicant's specification at page 23, lines 3-17. Certainly, no undue experimentation would be required in include, for example, a CH2 domain or a polyhistidine tag sequence to a polypeptide containing at least two CH3 IgE domains and a CH4 IgE domain that is heterologous to at least one of the CH3 IgE domains. Thus, one skilled in the art would have been able to make and use a polypeptide comprising heterologous CH3 and CH4 IgE domains without undue experimentation.

On page 3 of the Office Action, the Examiner cited the Nechansky *et al.* reference (*Int. Arch. Allergy Immunol.*, 120(4):295-302 (1999)) as teaching that "the synthesis of a recombinant single Cε3 domain still being able to bind to FcεRI with high affinity has *never* been successful" (emphasis in original). On page 4 of the Office Action, the Examiner also cited the Abaza *et al.* reference (*J. Protein Chem.*, 11:433-444 (1992)) as teaching that "even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with an antibody against that site." These references, however, do not change the fact that no undue experimentation is needed for one skilled in the art to obtain heterologous CH3 and CH4 IgE

segments, to combine them to make a polypeptide, and to determine whether the polypeptide induces an anti-self IgE response in a mammal. Further, the teachings of the Nechansky *et al.* reference are irrelevant since the presently claimed polypeptides are not required to have a CH3 domain that is able to bind with high affinity to an IgE receptor.

Given the above remarks and all the relevant material as a whole, Applicant respectfully submits that the specification fully enables the present claims. Thus, Applicant respectfully requests withdrawal of this rejection of claims 25-28 under 35 U.S.C. § 112, first paragraph.

The Examiner rejected claims 25-28 under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to reasonably convey to a person of skill in the art that Applicant was in possession of the claimed invention at the time the application was filed. The Examiner stated that the specification does not reasonably provide a written description of *all* polypeptides as set forth in claims 25-28 wherein the CH3 and CH4 domains are in any order for inducing an anti-self IgE response in any mammal. The Examiner also stated that the open-ended term "comprising" expands the polypeptides to include other amino acids at either or both ends, and that there is insufficient written description as to which undisclosed amino acids are to be added. The Examiner further stated that "[a]dequate written description requires more than a mere statement that it is part of the invention. The amino acid sequence itself is required." The Examiner concluded that "[w]ithout the amino acid sequence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed polypeptide looks like."

Applicant respectfully disagrees. The test for determining compliance with the written description requirement is whether the disclosure of an application describes the invention so that one skilled in the art reasonably can conclude that the inventor had possession of the claimed invention at the time of filing. *See, e.g., Vas-Cath, Inc. v. Mahhurkar*, 935 F.2d 1555, 1560 (Fed. Cir. 1991). Further, for claims drawn to a genus, the written description requirement may be satisfied through sufficient description of a representative number of species, which does not require the specification to provide individual support for each and every species that the genus embraces. *See, e.g., In re Angstadt*, 537 F.2d 498, 502 (Cust. & Pat. App. 1976), in which the

court decided that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art."

Claims 25-28 recite polypeptides containing at least two CH3 IgE domains and a CH4 IgE domain, wherein the CH4 IgE domain is heterologous to at least one of the CH3 IgE domains. Applicant's specification adequately describes the claimed polypeptides. For example, the term "IgE" used throughout the specification and in the claims is a descriptive term that not only discriminates IgE polypeptides from all other polypeptides but also discriminates IgE polypeptides from IgA, IgD, IgM, and IgG polypeptides. A skilled artisan familiar with Ig polypeptides at the time Applicant filed would not have confused an IgE polypeptide with any other polypeptide including IgA, IgD, IgM, and IgG polypeptides. One reason for this is that IgE polypeptides were well known at the time Applicant filed. In fact, IgE sequences from human, rat, mouse, pig, sheep, horse, dog, chimpanzee, orangutan, and opossum were known at the time Applicant filed as evidenced by Applicant's specification and the Aveskogh *et al.* reference. One of ordinary skill in the art reading Applicant's specification would have appreciated that the words used in Applicant's specification and claims alone fully describe and set forth Applicant's invention. In fact, a person having ordinary skill in the art at the time Applicant filed would have appreciated from Applicant's specification that Applicant invented the subject matter recited in claims 25-28.

Further, Figures 1 and 2 of Applicant's specification provide the primary amino acid structures of a plurality of IgE polypeptides. For example, these figures set forth the amino acid sequences of CH3 and CH4 IgE domains from human, rat, mouse, pig, and dog, opossum, and platypus. In fact, Figure 2 provides an alignment of the primary amino acid structure of opossum and platypus IgE, thereby describing common structural attributes between opossum and platypus IgE. These disclosed structural attributes are representative of the genus of non-placental mammalian IgE sequences as evidenced by the fact that the structure of platypus IgE is such that a nucleic acid fragment of platypus IgE was used to obtain an IgE sequence from another non-placental mammal, echidna, via standard library screening techniques based on hybridization. *See, e.g.*, Dr. Hellman's declaration. Given the disclosure of these IgE sequences, a person having ordinary skill in the art would have appreciated that Applicant adequately described a representative number of species to demonstrate compliance of the written

description requirement. As noted above, the description of a representative number of species does not require Applicant's specification to provide individual support for each and every species that the genus embraces, as the Examiner appears to contend.

In addition, Applicant's specification at page 26, lines 19-29 describes the structure of ORORO and 6his-ORRRORO-6his polypeptides. Given that Applicant's specification at page 15, lines 11-12 discloses that rat IgE domains of the disclosed polypeptides can be replaced with human IgE domains, Applicant's specification also describes OHOHO and 6his-OHHHOHO-6his polypeptides. Thus, given the described polypeptides and the description provided in the remainder of Applicant's specification, one of ordinary skill in the art would have appreciated that Applicant invented the presently claimed invention. Thus, Applicant's specification fully satisfies the written description requirement.

To support the allegation that Applicant was not in possession of the claimed genus of polypeptides, the Examiner referred to *Regents of University of California v. Eli Lilly & Co.* (119 F.3d 1559, 43 USPQ2d 3998 (Fed. Cir. 1997)) and *University of Rochester v. G.D. Searle & Co.* (358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir. 2004)). *See*, page 5 of the outstanding Office Action. Applicant notes, however, that the court, while ruling in the Lilly case that one cDNA sequence does not provide sufficient written description of a genus of cDNA sequences, stated the following: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus . . ." In contrast to the specification at issue in the Lilly case, Applicant's specification provides a plurality of examples of amino acid sequences that could be included in the claimed polypeptides, or could be used to obtain amino acid sequences from other species for inclusion in the claimed polypeptides. Applicant also notes that in the Rochester case, the patent at issue claimed a method of achieving a biological effect, but disclosed no compounds that could accomplish that effect, and thus the patent was deemed invalid for lack of written description. Again, in contrast to the Rochester case, Applicant's specification discloses multiple examples of IgE amino acid sequences that can be included in the claimed polypeptides, and also discloses multiple examples of chimeric polypeptides containing at least two CH3 IgE domains and at least one heterologous CH4 IgE domain. Thus, the holdings of the cited cases do not alter the fact that the present claims are adequately described by Applicant's specification.

In light of the above, Applicant respectfully requests withdrawal of this rejection of claims 25-28 and 36 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicant submits that claims 25-28 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please apply the $60 Petition for Extension of Time fee, as well as any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

Date: March 30, 2005

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